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(54) Anti-inflammatory compositions exhibiting minimized gastric damage.

(57) Anti-inflammatory/analgesic compositions containing combinations of salicylate-derived anti-inflammatory drugs, such as acetylsalicylic acid, together with adenosine derivatives are disclosed. These compositions reduce the quantity and severity of gastric damage which frequently accompanies treatment with salicylate derivatives, without adversely effecting the desirable pharmacological properties of the salicylates. The method of minimizing gastric damage induced by anti-inflammatory salicylate-derived compounds, using adenosine derivatives, is also disclosed.

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ANTI-INFLAMMATORY COMPOSITIONS EXHIBITING
MINIMIZED GASTRIC DAMAGE

The present invention relates to pharmaceutical compositions, especially those administered orally, which provide effective anti-inflammatory and analgesic treatment while minimizing the gastric damage which is a frequent side effect of such treatment.

Inflammation, or the "inflammatory response", is the result of complex interconnected physiological events, including increased vascular permeability, fluid accumulation, and the migration of a changing population 10 of inflammatory cells into the afflicted area. The clinical manifestations of inflammation include swelling (edema), increased local temperature, erythema, and pain. The inflammatory response can be triggered by any of numerous causative factors, including certain bacteria, 15 radiation, hypersensitivity to chemical agents, and arthritis-like conditions. The inflammatory response is generally believed to be a primary defense mechanism in the body but, when left unchecked, it can become excessive and result in pain and functional impairment.

20 A great variety of anti-inflammatory and analgesic drugs, especially the salicylates such as aspirin and aspirin derivatives (which are by far the most widely-used anti-inflammatory/analgesic agents), are known and used to combat inflammation and its attendant pain.

25 These compounds are frequently used to relieve the pain

and inflammation associated with chronic conditions, such as bursitis and arthritis. Frequently, however, such compounds exhibit, as a highly undesirable side effect, the propensity to cause gastrointestinal irritation ranging 5 from upset stomach to gastric lesions and bleeding. These side effects are particularly troublesome in the treatment of chronic conditions where prolonged use of high dosage levels, frequently of aspirin or aspirin derivatives, are often prescribed. Thus, the desirability of formulating 10 compositions having a high level of anti-inflammatory and analgesic activity, but with a greatly reduced propensity to cause gastrointestinal damage, i.e., a "non-ulcerating aspirin", is clear.

Gastrointestinal irritation is a well-known side 15 effect of a wide range of non-steroidal anti-inflammatory agents. See Scherrer and Whitehouse, Antiinflammatory Agents, Vol. 1, Academic Press, New York, 1974, pages 181-182. Thus, Rainsford, et al., Pharm. Res. Comm., 12(1), 85-95 (1980), describe a series of tests to determine the 20 ulcerogenicity and efficacy of a group of aspirin-derived products; based on these tests, it is suggested that aspirin damage to the gastrointestinal tract can be reduced by supplying the aspirin together with a source of metabolites (e.g., D-glucose, citrate or acetate) directly to the 25 gastric mucosa. Rainsford, et al., Biochem. Pharm., 29, 1281 (1980), teach that ulceration damage caused by aspirin or other non-steroidal anti-inflammatory drugs can be reduced by combining those drugs with adjunct components which serve as: (1) buffers to neutralize drug acidity; 30 (2) solubilizers of acidic drugs; or (3) certain nutrients, such as glucose and/or acetate. Asker, et al., Pharmazie, 31, 728-30 (1976) show that complexation between aspirin and adenosine or ATP can occur in vitro under conditions

of neutral pH. They postulate that such complexes, if formed in vivo, might contribute to the prolongation of aspirin-induced gastrointestinal bleeding by reducing aggregation of platelets induced by ATP. See also Asker,
5 et al., J. Pharm. Sci. 63, 966-67 (1974).

Adenosine and adenosine phosphates are postulated as being useful for a variety of therapeutic applications. Thus, for example, adenosine has been used to treat psoriasis (German Specification 2,401,450); adenosine has
10 been used to stimulate insulin secretion (Feldman, et al., Endocrinology, 94(2), 388-394 (1974)); ATP has been used in combination with pyridoxal hydrochloride to treat air sickness (Russian patent 374,086-S); cyclic-AMP has been used as an anti-inflammatory agent (German Specification
15 2,732,179); and adenosine and its nucleotides, e.g., AMP, are known as vasodilators (French patent 3,249M). U.S. Patent 3,089,869, issued May 14, 1963 and assigned to Laboratoire d'Analyses et de Recherches, describes a general method for producing organic acid esters of adenine phosphates, such as the ester of aspirin with AMP.
20

Szreniawski, Acta Physiologica Polonica (Warzawa), 3:3, 363-374 (1952), suggests that adenosine, administered subcutaneously, may protect against histamine-induced ulceration in guinea pigs, a commonly accepted animal model
25 for peptic ulcers. However, materials which show activity in peptic ulcer animal models do not necessarily have any efficacy against aspirin-induced damage in animals, let alone aspirin-induced ulcerations in humans. This is true, in part, because the etiologies of peptic ulcers and
30 aspirin-induced gastric damage are entirely different.

While the etiology of peptic ulcer disease is not completely understood and probably differs significantly between gastric and duodenal peptic ulcers, there are several physiological and non-physiological predisposing factors
35 involved in peptic ulcers that do not play a significant role in aspirin-induced gastric damage. Examples of these

factors are: abnormal high (duodenal ulcers) or abnormal low (gastric ulcers) rates of acid secretion, abnormal gastric motility, a mucosa barrier weakened and made susceptible to acid and/or pepsin attack by external factors, such as physical or psychological stress, smoking, alcohol, certain foods or by genetic factors. In contrast, aspirin-induced damage occurs under normal physiological stomach conditions because of the ability of aspirin to diffuse into the cells of the gastric mucosa impairing their normal protective function.

An example of a drug that shows selective activity is carbeneoxolone sodium, which is not active against aspirin-induced ulcers in rats (Yeomans, et al., Digestive Diseases, 19, 217 (1974), but is active in other animal models (Lea and Bianchi in Peptic Ulcers, ed. by C.J. Pfeiffer, pp. 329-48, Lippincott Co., Philadelphia, 1971) and, further, is clinically proven to be effective against duodenal (Nagy, Gastroenterology, 74, 7 (1978) and gastric (Pinder, et al., Drugs, 11, 245 (1976) ulcers in humans. Similarly, cimetidine, presently the most commonly used peptic ulcer therapy, does not show activity in all animal models (Okabe, et al., Dig. Diseases, 22, 677, (1977)).

Finally, French Patent 1894M, published March 7, 1966 by Société Anonyme Magsifer, describes combinations of aspirin with adenosine monophosphate, adenosine di-phosphate, and adenosine triphosphate in weight ratios of about 1:1; it is taught that any of such combinations permit the dosage of aspirin to be reduced by about 50% without hurting its therapeutic benefits.

It has now been found that by combining salicylate-derived anti-inflammatory drugs, such as aspirin, with specifically-defined purine derivatives, especially adenosine, within a narrow range of weight ratios, the gastric ulceration caused by the anti-inflammatories is dramatically reduced without impairing the therapeutic efficacy of the compositions.

It is, therefore, an object of the present invention to formulate effective anti-inflammatory/analgesic compositions, especially for oral use.

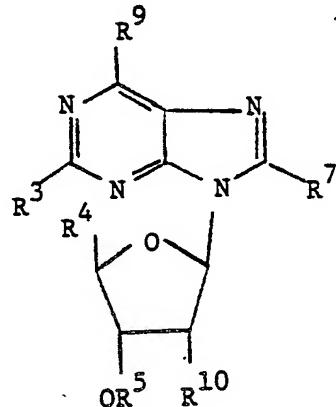
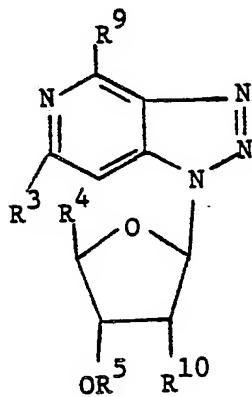
It is a further object of the present invention to 5 formulate anti-inflammatory/analgesic compositions which exhibit minimized gastric damage side effects.

It is a still further object of the present invention to provide a method for minimizing the undesirable 10 gastrointestinal side effects which frequently accompany treatment with salicylate-derived anti-inflammatory drugs.

The present invention embraces pharmaceutical compositions, particularly for oral administration, which provide anti-inflammatory and analgesic benefits while 15 minimizing gastric damage, comprising:

- (a) a safe and effective amount of a salicylate-derived anti-inflammatory drug; and
- (b) a safe and effective amount of a purine derivative selected from the group consisting of

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and mixtures thereof, wherein R¹ and R² are each selected from H, C₁-C₄ alkyl and phenyl; R³ and R⁷ are each selected from H, C₁-C₄ alkyl,

-NR¹R², -OCH₃, -SCH₃, -NHCOCH₃, -OH, -Cl and -Br;

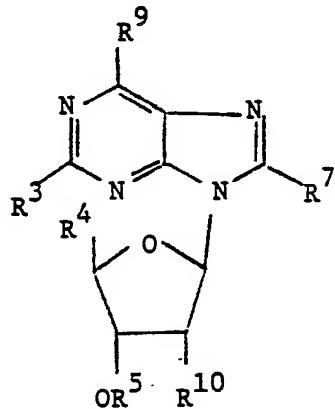
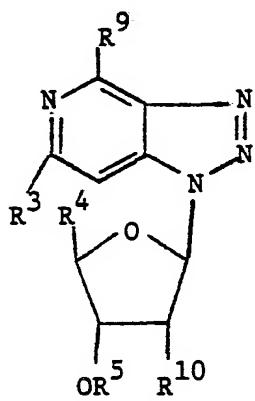
5 R⁴ is selected from -CNR⁵R⁶, -COR⁵, and -CH₂(OR⁵);
R⁵ is selected from H, C₁-C₄ alkyl and PO₃H₂;
R⁶ is selected from H and C₁-C₄ alkyl; R⁹ is selected from -NR¹R² and -NO; and R¹⁰ is selected from H and -OR⁵; and

10 wherein the ratio of salicylate derivative to purine derivative, by weight, is from about 10:1 to about 1:4, preferably from about 7:1 to about 1:1, most preferably from about 6:1 to about 2:1.

Preferred purine derivatives include adenosine,
15 adenosine-5'-monophosphate (AMP), adenosine-N¹-oxide,
8-bromoadenosine, 8-azaadenosine, 2'-deoxyadenosine, 2',3'-isopropylidine adenosine, and mixtures thereof; adenosine is particularly preferred.

The present invention also encompasses a method for
20 minimizing anti-inflammatory-induced gastric damage comprising the administration to a person or animal under treatment with salicylate-derived anti-inflammatory drugs of from 10 to about 4,000 milligrams of a purine derivative having the formula

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and mixtures thereof, wherein R¹ and R² are each selected from H, C₁-C₄ alkyl and phenyl; R³ and R⁷ are each selected from H, C₁-C₄ alkyl, -NR¹R², -OCH₃, -SCH₃, -NHCOCH₃, -OH, -Cl and -Br; R⁴ is selected from -CNR⁵R⁶, -COR⁵, and 5 -CH₂(OR⁵); R⁵ is selected from H, C₁-C₄ alkyl and PO₃H₂; R⁶ is selected from H and C₁-C₄ alkyl; R⁹ is selected from -NR¹R² and -NO; and R¹⁰ is selected from H and -OR⁵; in an amount such that the weight ratio of anti-inflammatory drug to purine derivative is from about 10:1 to about 1:4, said 10 purine derivative being administered concurrently with said anti-inflammatory drug or no more than about 30 minutes, preferably no more than about 20 minutes, and most preferably no more than about 10 minutes, prior thereto.

DETAILED DESCRIPTION OF THE INVENTION

15 The compositions and treatment regimens of this invention employ: (1) specifically-defined adenosine derivatives in combination, within a narrow range of weight ratios, with (2) salicylate-derived anti-inflammatory, analgesic and/or anti-pyretic drugs. These components will 20 be described in detail hereinafter. The compositions are administered to alleviate inflammation and/or pain in patients, while minimizing the undesirable gastrointestinal side effects which frequently accompany such treatment.

By "safe and effective amount of a salicylate-derived anti-inflammatory drug", as used herein, is meant sufficient compound to alleviate tissue inflammation and/or its accompanying pain, at a reasonable benefit/risk ratio attendant with any medical treatment, when used in the manner of this invention. Within the scope of sound

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medical judgment, the dosage of anti-inflammatory compound will vary with the particular condition being treated, the severity of the condition, the duration of the treatment, the physical condition of the patient, and the specific 5 anti-inflammatory compounds employed. As used herein, the term "anti-inflammatory compound" also includes pharmaceuticals which deliver analgesic and/or anti-pyretic benefits.

By "safe and effective amount of a purine derivative", as used herein, is meant sufficient compound to minimize gastrointestinal damage, at a reasonable benefit/risk ratio attendant with any medical treatment, when used in the manner of this invention. Within the scope of sound 10 medical judgment, the dosage of purine derivative will vary 15 with the physical condition of the patient, the duration of the treatment, the specific purine derivatives employed, and the specific anti-inflammatory compounds employed.

By "pharmaceutically-acceptable", as used herein, is meant that the drug compounds and other ingredients used in 20 the present compositions and processes are suitable for use in contact with the tissues of human and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio.

25 The term "administration" of the compositions herein includes systemic use, as by injection, intravenous infusion, suppositories and, preferably, the oral administration thereof, as well as topical application of the compositions to the afflicted situs.

By the term "comprising", as used herein, is meant 30 that various additional compatible drugs and medicaments, as well as inert ingredients, can be conjointly employed in the compositions and processes of this invention, as long as the critical salicylate-derived anti-inflammatory drugs and purine derivatives are used in the manner disclosed.

The term "comprising" thus encompasses and includes the more restrictive terms "consisting of" and "consisting essentially of" which characterize the use of the essential anti-inflammatory and purine derivative compounds.

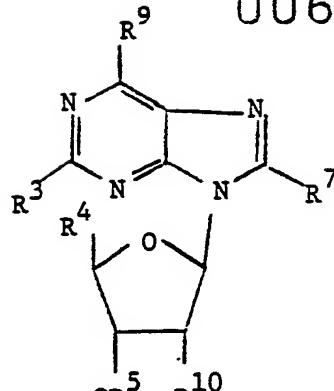
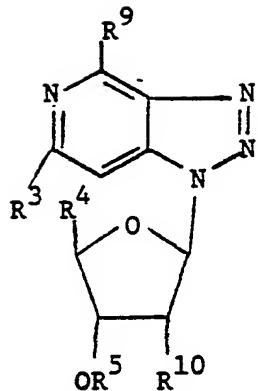
5 By "compatible", as used herein, is meant that the components of the compositions are capable of being commingled without interacting in a manner which would substantially decrease the efficacy of the total compositions under ordinary use situations.

10 By "carrier", as used herein, is meant a liquid, fluid or solid material which can optionally be used to provide finished compositions of the present invention for systemic, oral or topical administration.

15 All percentages herein are by weight, unless otherwise specified.

The purine derivatives useful in the compositions of the present invention are adenosine and specific derivatives of adenosine. These compounds are well-known compounds and are present in everyday biological processes. It is, however, important to note that selection of the particular purine derivatives as defined herein is critical to achieving the desired minimization of gastric damage; thus, closely related compounds, such as guanine, guanosine, guanosine derivatives, and cyclic AMP, are not useful in the compositions of the present invention.

20 1,N⁶-ethenoadenosine (VI), ADP (adenosine-5'-diphosphate) and ATP (adenosine-5'-triphosphate) work only at relatively high dosage levels (e.g., anti-inflammatory: purine ratios from about 1:1.5 to about 1:4), making their inclusion together with the salicylate compounds in a single dosage form impractical. Adenine does work to minimize gastrointestinal damage induced by non-steroidal anti-inflammatory drugs, but is not included in the present invention since it does not fall within the necessary toxicity limits. The purine derivatives (I and II) which may be used in the present invention are those having the formulae:



and mixtures thereof, wherein R^1 and R^2 are each selected from H, C_1-C_4 alkyl and phenyl, and are preferably hydrogen; R^3 and R^7 are each selected from H, C_1-C_4 alkyl, $-NR^1R^2$,

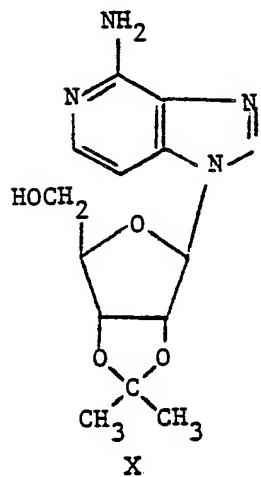
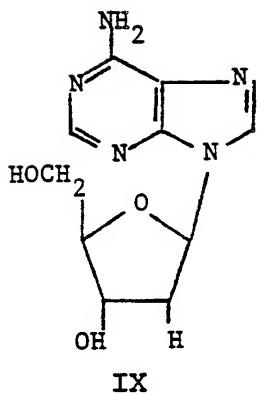
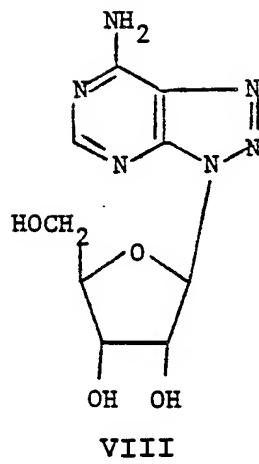
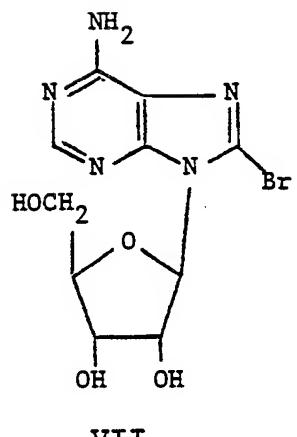
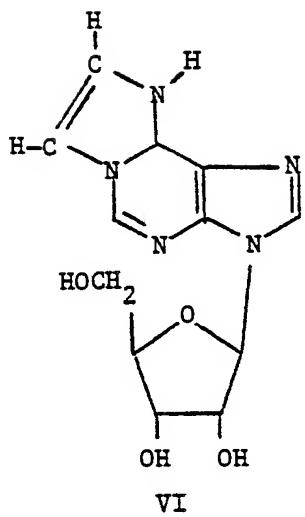
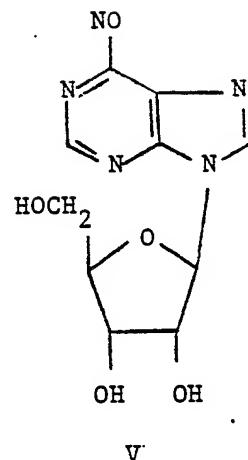
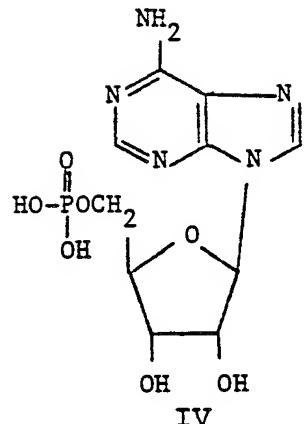
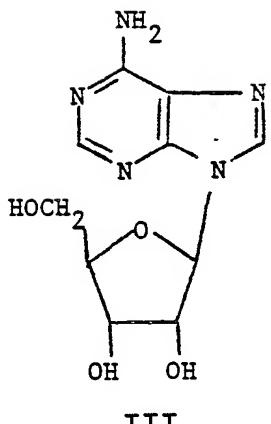
5 $-OCH_3$, $-SCH_3$, $-NHCOCH_3$, $-OH$, $-Cl$ and $-Br$, with hydrogen

being preferred; R^4 is selected from $-CNR^5R^6$, $-COR^5$, and, preferably, $-CH_2(OR^5)$; R^5 is selected from H, C_1-C_4 alkyl and PO_3H_2 (preferably H or PO_3H_2); R^6 is selected from H and C_1-C_4 alkyl (preferably H); R^9 is selected from $-NR^1R^2$ 10 and $-NO$ (preferably $-NR^1R^2$); and R^{10} is selected from H and $-OR^5$. R^1 and/or R^2 may form a ring structure which connects the N^6 with the nitrogen at position 1 (e.g., 1, N^6 -ethenoadenosine). The R^5 and/or R^{10} groups may also be combined to form a ring structure connecting the 2' and 15 3' carbon atoms (e.g., 2',3'-isopropylidene adenosine).

Preferred purine derivatives for use in the compositions of the present invention include adenosine (III), adenosine monophosphate (IV), adenosine $-N^1$ -oxide (V), 8-bromo-20 adenosine (VII), 8-azaadenosine (VIII), 2'-deoxyadenosine (IX), and 2',3'-isopropylidene adenosine (X).

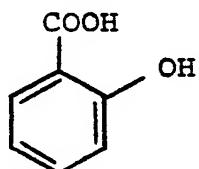
Particularly preferred purine derivatives are adenosine and adenosine monophosphate, with adenosine being most preferred for use in the present invention. These purine derivatives are described in greater detail in Lehninger, 25 Biochemistry, Worth Publishers, New York, 1975, pp. 309-317, incorporated herein by reference. In general, greater purity of the purine derivatives used results in better protection against gastric damage.

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Any salicylate-based anti-inflammatory, analgesic or anti-pyretic drug known in the art, especially those having gastrointestinal irritation side effects commonly associated with them, or mixtures of such drugs may be used 5 in the present invention. Of course, the anti-inflammatory drugs chosen must be compatible with the particular purine derivatives used. The salicylate-based compounds used herein comprise salicylic acid and derivatives thereof. Salicylic acid (o-hydroxybenzoic acid) is represented by 10 the formula

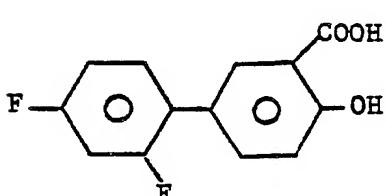


and can be derivatized at both the hydroxyl and carboxyl groups to provide various pharmacologically-active analgesic and/or anti-inflammatory agents. The salicylate-based compounds employed in the practice of this invention 15 are well-known in the medical arts and their anti-inflammatory and analgesic activity in humans and lower animals is well documented; they are widely used and are known to be gastrointestinal irritants.

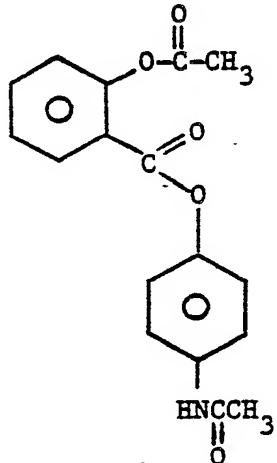
20 Salicylic acid, its pharmaceutically-acceptable salts, esters, and derivatives are useful herein; they are disclosed in detail in Scherrer and Whitehouse, Antiinflammatory Agents, Vol. 1, Academic Press, New York, 1974, pp. 75-82, incorporated herein by reference. Such materials 25 include, for example, magnesium salicylate, acetylsalicylic acid (aspirin; especially preferred for use herein along with its pharmaceutically-acceptable salts and esters), aloxiiprin (a polymeric condensation product of aluminum oxide and aspirin), calcium carbaspirin (calcium acetyl- 30 salicylate-urea complex), choline magnesium trisalicylate,

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salicylsalicylic acid, diflunisal (formula XI, below), and benoylate (acetaminophen ester of aspirin; formula XII, below). All of the foregoing materials are commercially available and are well-recognized for use as anti-inflammatory and analgesic agents.



XI



XII

In order to provide the desired minimization of gastric damage, the salicylate-derived anti-inflammatory drugs and purine derivatives utilized in the present invention must be used within a narrow range of weight ratios. Thus, in formulating compositions the ratio of anti-inflammatory drug to purine derivative, by weight, is from about 10:1 to about 1:4, preferably from about 7:1 to about 1:1, more preferably from about 6:1 to about 2:1. Where AMP is the purine derivative being utilized, because of activity and dosage size considerations, for optimum performance it is preferred that the ratio, by weight, of salicylate anti-inflammatory drug to AMP be from about 1:1.5 to about 1:4.

The compositions of the present invention may be formulated in any standard dosage form; however, the

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invention is particularly beneficial when it is formulated for oral ingestion, for example, in the form of tablets, capsules, lozenges, liquids, emulsions, or pills. In producing a unit dosage form of the compositions of the 5 present invention, each dosage contains from about 100 to about 2000, preferably from about 200 to about 750, milligrams of the anti-inflammatory drug together with from about 10 to about 2000, preferably from about 20 to about 1000, and most preferably from about 35 to about 750, 10 milligrams of the purine derivative. The dosage forms may, in addition to the required components, contain additional compatible pharmaceutically-active materials, in safe and effective amounts, as well as adjunct formulation-type components conventionally used in the preparation of phar- 15 maceutical formulations, such as, carriers, excipients, anti-oxidants, tablet disintegrating agents, preservatives, colorings, flavors, stabilizers, fillers, and diluents, at their art-established usage levels.

In its method of treatment aspect, the present in- 20 vention provides a means for minimizing gastric irritation and damage to persons or animals under treatment with salicylate-derived anti-inflammatory drugs, as defined hereinbefore. In practicing this method, from about 10 to about 4000 milligrams, preferably from about 20 to about 25 2000 milligrams, and most preferably from about 35 to 750 milligrams, of adenosine or adenosine derivatives, as defined and preferred above (formulae I and II), are ad- ministered either concurrently with or no more than about 30 minutes, preferably no more than about 20 minutes, and 30 most preferably no more than about 10 minutes, prior to the administration of the anti-inflammatory drug. In the most preferred aspect of the method of treatment, the anti- inflammatory drug and the purine derivative are admin- 35 istered (in any order) simultaneously (that is, within about 0 to 2 minutes of each other). Surprisingly, effec- tive protection against salicylate anti-inflammatory drug- induced gastrointestinal irritation is not obtained when

the purine derivative is administered as quickly as 10 minutes after the administration of the anti-inflammatory drug. When the anti-inflammatory agents and purine derivatives are administered separately (i.e., not as a single 5 unit dose), it is preferred that the anti-inflammatory agent be delivered orally, while the purine derivative may be delivered in any conventional manner, preferably parenterally or orally, most preferably orally. Purine derivatives preferred for use in the method of treatment aspect 10 of the present invention include adenosine, adenosine monophosphate, adenosine diphosphate, adenosine-N'-oxide, 1,N⁶-ethenoadenosine, 8-bromoadenosine, 8-azaadenosine, 2'-deoxyadenosine, 2',3'-isopropylidene adenosine, and mixtures thereof.

15 The following non-limiting examples illustrate the compositions and the methods of treatment embodied in the present invention.

EXAMPLE I

20 The following experiments demonstrate the protective effect of adenosine and adenosine derivatives against aspirin-induced gastric lesions; in addition, these experiments demonstrate that no such protection is obtained when the adenosine derivatives utilized fall outside of those defined in the present application.

25 For these experiments, the test materials were suspended in 0.5% methyl cellulose aqueous solutions. The pH of the aspirin solution was 2.7 and the pH of the solutions containing the purine materials was adjusted to pH 2.7 using HCl.

30 Male Sprague-Dawley rats were obtained (approximate weight = 150 grams each) and allowed to acclimate for at least 4 days. During this period the animals were allowed Purina Rat Chow and tap water ad libitum. The animals were food fasted about 18 hours prior to dosing; during this 35 period water was provided ad libitum.

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The rats were dosed by oral gavage using a #8 catheter attached to a 1 cc syringe. The animals were dosed and sacrificed according to a predetermined schedule (the dosing order was determined at random prior to starting each experiment). After dosing, the animals were also water fasted.

The rats were sacrificed, either by CO₂ inhalation or cervical dislocation, two hours after dosing. Their stomachs were removed intact and placed on plastic-backed absorbent paper. The stomachs were then opened along the greater curvature, the fundus and esophagus were removed and the stomach was spread over a piece of white cardboard, using cotton-tipped applicators to level the rugae. The stomachs were then examined, using a dissecting microscope at 7X magnification, and the length of each lesion present was determined using a calibrated reticule.

The effect of adenosine on aspirin-induced gastric lesions is shown in Table 1. In these experiments, the aspirin and adenosine were dosed simultaneously. In this table, N indicates the number of rats tested for the stated dosage.

Table 1
EFFICACY OF ADENOSINE

			Lesion Length (mm) ± SEM	% Reduction from ASA Controls
25	<u>Treatment</u>	<u>N</u>		
	125 mg/kg aspirin (control)	142	30.4 ±3.1	-
30	125 mg/kg aspirin + 25 mg/kg adenosine	37	10.6 ±1.4	65.1*
	125 mg/kg aspirin + 62.5 mg/kg adenosine	38	4.6 ±0.9	84.8*
	125 mg/kg aspirin + 125 mg/kg adenosine	124	2.5 ±0.7	91.6*

35 * P<0.05

In addition to adenosine, several other purine derivatives (some falling inside and some falling outside the definition of purine derivatives required herein 1.4

were evaluated in experiments similar to the one described above. The lesions of the aspirin plus purine derivative were compared to a control group receiving 125 mg/kg of aspirin alone. The protective ability of these various 5 purine materials are shown in Table 2, expressed as percent reduction of lesions compared to the control.

Table 2

Reduction of Aspirin-Induced Gastric
Lesions by Purine Derivatives Other than Adenosine

	<u>Compound</u>	<u>N</u>	<u>Dose mg/kg</u>	<u>% Reduction in Lesions</u>
10	Adenosine-5'-diphosphate (ADP)	10	125	50
		10	250	82.5*
15	Adenosine-5'-triphosphonate (ATP)	10	125	25
	Adenosine-5'-monophosphate (AMP)	18	155	79*
	Adenosine-N ¹ -oxide	10	80	.59
	1,N ⁶ -ethenoadenosine	10	125	75*
	1-methyl adenosine	8	125	50*
	6-methyl adenosine	10	25	16
20	8-bromoadenosine	10	25	- 9
	8-aminoadenosine	10	125	76*
	8-azaadenosine	10	125	19
	2'-deoxyadenosine	10	125	60*
	3'-deoxyadenosine	8	125	64*
25	2',3'-isopropylidine adenosine	18	125	-47
	5'-deoxy-5'-methylthioadenosine	10	125	95*
	2'-deoxy-adenosine-5'-mono- phosphate	10	125	-102*
	Adenine	20	125	16
30	Guanosine	30	125	94*
	Hypoxanthine	10	125	41
	Inosine	10	125	13
	Allantoin	10	125	18
				30

*P<0.05

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In other experiments aspirin and adenosine were dosed at separate times. The results of these experiments indicated that while adenosine was most protective when dosed simultaneously with aspirin (about 90% reduction in lesions), it was also effective when dosed 30 minutes (about 45% lesion reduction) or 10 minutes (about 60% lesion reduction) prior to administration of the aspirin. In sharp contrast, administering the adenosine 10 minutes after the aspirin is ingested yielded less than a 10% reduction in lesions. In these experiments, both the aspirin and the adenosine were administered in dosages of 125 mg/kg.

Parenteral administration of adenosine was also found to be protective against aspirin-induced gastric damage, as illustrated by the following experiment.

Rats, chosen and prepared as above, were dosed with i.p. injections of adenosine in 0.9% sterile physiological saline solution, adjusted to pH 7 with 1N NaOH. The adenosine solution was injected 15 minutes prior to an oral dose of 125 mg/kg aspirin. The results of this experiment are shown in Table 3.

Table 3

<u>Treatment</u>	<u>N</u>	<u>Average Lesion Length (mm) ± SEM</u>	<u>% Red.</u>
125 mg/kg aspirin (p.o.)	10	36.1 ±10.8	-
25 125 mg/kg aspirin (p.o.) plus 93.7 mg/kg adenosine (i.p.)	10	6.2 ±7.9	83*
125 mg/kg aspirin (p.o.) plus 47.6 mg/kg adenosine (i.p.)	10	24.1 ±6.5	33

*P < 0.05

In addition to reducing macroscopic lesions in the stomach produced by aspirin ingestion, adenosine was also found to reduce occult blood loss from the G.I. tract of

rats. In these experiments, male Sprague-Dawley rats were injected i.v. with ⁹⁵Fe labeled ferrous citrate. Eight days after injection, feces were collected for 24 hours to establish base line data. The rats were then dosed orally 5 with aspirin or aspirin-adenosine mixtures, as suspensions in 0.5% methylcellulose, and the feces were again collected for 24 hours. The rats were fasted during the 24-hour pre-dose period and for 2 hours after drug dosing. Results are shown in Table 4.

10

Table 4

<u>Treatment</u>	<u>Dose (mg/kg)</u>		N	Blood Loss in 24 hrs. (μ l) + S.D.
	Aspirin	Adenosine		
Aspirin	125	0	7	158 ± 46
Aspirin + Adenosine	125	125	6	76* ± 11
15 Aspirin	300	0	10	198 ± 131
Aspirin + Adenosine	300	300	10	98* ± 29
Aspirin	300	0	10	224 ± 98
Aspirin + Adenosine	300	60	10	148* ± 32
Aspirin + Adenosine	300	30	10	135* ± 43

20 *p < 0.05

Aspirin-induced damage in dogs was also reduced by concurrent dosing of adenosine and aspirin as indicated in the following experiment.

Fasted male beagles were orally dosed with tablets 25 of aspirin, aspirin plus adenosine, or aspirin plus cimetidine. The aspirin and adenosine were dosed simultaneously. The cimetidine was dosed approximately 1 hour before the aspirin; the dose level of cimetidine was 5 times that needed to give a 90% reduction in acid secretion. Approximately 19 hours later, the dogs were again dosed and 4 hours later their stomachs were examined by endoscopy. The incidence of erosions was recorded and the overall gastric damage assessed subjectively, using an arbitrary grading scale. The results are shown in Table 5.

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Table 5

<u>Treatment</u>	<u>Avg. Aspirin</u>	<u>Dose (mg/kg)</u>	<u>Cimetidine</u>	<u>N</u>	<u>Avg. Incidence of Erosions</u>	<u>Avg. Damage Grade</u>	<u>% Reduction in Damage</u>
5 Aspirin	97.8	0	-	5	80%	16	-
Aspirin + Adenosine	100	100	-	5	20%	7	56
Aspirin + Cimetidine	101	0	30	5	60%	12	33

Similar results to those observed above are obtained when the aspirin used in the above experiments is replaced, in whole or in part, by a biologically equivalent amount of magnesium salicylate, aloxiprin, calcium carbasprin, choline 5 magnesium trisalicylate, salicylsalicylic acid, diflunisal, benoylate, or pharmaceutically-acceptable salts or esters of these compounds. Similar results are also observed where the adenosine used in the above experiments, is replaced, in whole or in part, by adenosine-5'-monophosphate, 10 adenosine-5'-diphosphate, adenosine-N¹-oxide, 1,N⁶-ethenoadenosine, 8-bromoadenosine, 8-azaadenosine, 2'-deoxyadenosine, or 2',3'-isopropylidine adenosine.

EXAMPLE II

Using conventional tabletting techniques well-known in 15 the pharmaceutical arts, tablet formulations, having the components and compositions listed below, are formulated. These tablets, when taken in a conventional manner (i.e., 2 tablets every 4 hours for an adult) provide effective anti-inflammatory and analgesic benefits with minimized 20 gastric damage.

1. 325 mg aspirin
 65 mg adenosine
 19.5 mg CLD-2 (tablet excipient with enhanced disintegration properties)
- 25 4 mg magnesium stearate
2. 325 mg aspirin
 325 mg adenosine
 32.5 mg starch
 55 mg stearic acid
- 30 3. 325 mg aspirin
 162.5 mg adenosine
 19.5 mg carboxymethylcellulose
 5 mg hydrogenated vegetable oil

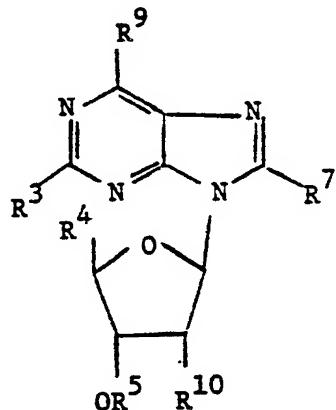
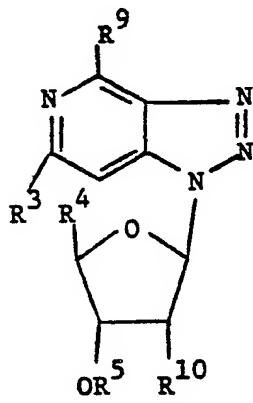
4. 325 mg aspirin
243.75 mg adenosine 5'-monophosphate
28.25 mg starch
6 mg stearic acid
- 5 5. 325 mg aspirin
325 mg 2',3'-isopropylidine adenosine
32.5 mg starch
6 mg stearic acid
6. 600 mg magnesium salicylate
- 10 120 mg adenosine
36 mg starch
7 mg magnesium stearate
7. 375 mg diflunisal
75 mg adenosine
- 15 22.5 mg CLD-2
4 mg magnesium lauryl sulfate
8. 325 mg adenosine
6 mg starch
4 mg lauric acid
- 20 9. 325 mg aspirin
65 mg adenosine
120 mg calcium carbonate
40 mg anhydrous citric acid
5 mg aluminum stearate
- 25 As an alternative method of administration, for injection, the adenosine or adenosine derivatives, listed above, are prepared in a normal physiological saline solution at an appropriate dosage concentration. This solution, when injected either simultaneously with or no more than 30 minutes before administration of salicylate-based anti-inflammatories, greatly decreases the amount of gastric damage caused by the salicylate-based compounds.

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CLAIMS

1. A pharmaceutical composition, providing an anti-inflammation and analgesic benefit together with minimized gastric damage, characterized in that it comprises:

- 5 (a) a safe and effective amount of a salicylate-derived anti-inflammatory drug; and
 (b) a safe and effective amount of a purine derivative selected from the group consisting of



10 and mixtures thereof, wherein R¹ and R² are each selected from H, C₁-C₄ alkyl and phenyl; R³ and R⁷ are each selected from H, C₁-C₄ alkyl,

$\text{-NR}^1\text{R}^2$, $-\text{OCH}_3$, $-\text{SCH}_3$, $-\text{NHCCCH}_3$, $-\text{OH}$, $-\text{Cl}$ and $-\text{Br}$;

15 R⁴ is selected from $-\text{CNR}^5\text{R}^6$, $-\text{COR}^5$, and $-\text{CH}_2(\text{OR}^5)$;

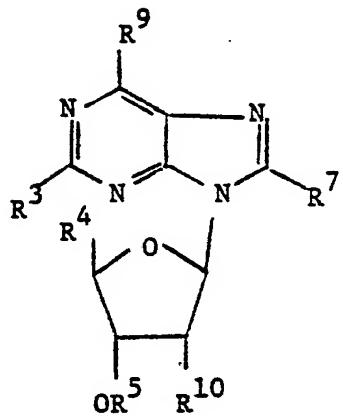
R⁵ is selected from H, C₁-C₄ alkyl and PO_3H_2 ;

R⁶ is selected from H and C₁-C₄ alkyl; R⁹ is selected from $-\text{NR}^1\text{R}^2$ and $-\text{NO}$; and R¹⁰ is selected from H and $-\text{OR}^5$; and

wherein the ratio of anti-inflammatory drug to purine derivative, by weight, is from 10:1 to 1:4.

2. A composition according to Claim 1 characterized in that the ratio, by weight, of anti-inflammatory drug to purine derivative is from 7:1 to 1:1.

3. A composition according to Claim 1 or 2 characterized in that the purine compound is an adenosine derivative having the



4. A composition according to any one of Claims 1-3 characterized in that the purine derivative is selected from the group consisting of adenosine, adenosine monophosphate, adenosine-N¹-oxide, 8-bromoadenosine, 8-azaadenosine, 2'-deoxyadenosine, 2',3'-isopropylidene adenosine, and mixtures thereof.

5. A composition according to any one of Claims 1-4 characterized in that the purine derivative is adenosine.

6. A composition according to any one of Claims 1-5 characterized in that the anti-inflammatory drug is selected from the group consisting of magnesium salicylate, acetylsalicylic acid, aloxiprin, calcium carbspirin, choline magnesium tri-salicylate, salicylsalicylic acid, diflunisal, benoylate, pharmaceutically-acceptable salts and esters of these compounds, and mixtures thereof.

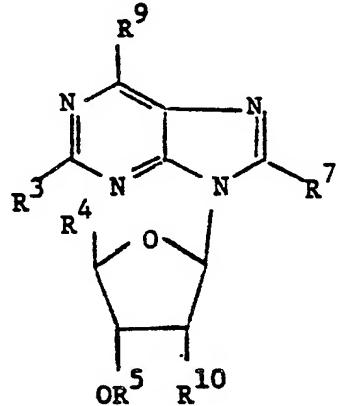
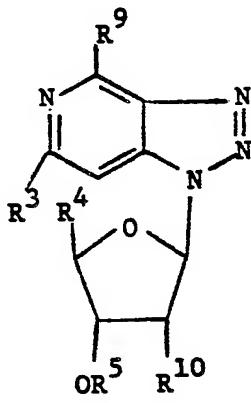
- 3 -

7. A composition according to any one of Claims 1-6 characterized in that the anti-inflammatory drug is acetylsalicylic acid or a pharmaceutically-acceptable salt or ester thereof.

8. A composition according to any one of Claims 1-7 characterized in that the ratio of anti-inflammatory drug to purine derivative, by weight, is from 6:1 to 2:1.

9. A composition according to Claim 1 characterized in that the purine derivative is adenosine monophosphate and the ratio of anti-inflammatory drug to purine derivative, by weight, is from 1:1.5 to 1:4.

10. A method for minimizing gastric damage characterized by the administration to a person or animal under treatment with salicylate-derivatized anti-inflammatory drugs of from 10 to 4000 milligrams of a purine derivative having the formula



and mixtures thereof, wherein R¹ and R² are each selected from H, C₁-C₄ alkyl and phenyl; R³ and R⁷ are each selected from H, C₁-C₄ alkyl,

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-NR¹R², -OCH₃, -SCH₃, -NHCOCH₃, -OH, -Cl and -Br;

15

R⁴ is selected from -CNR⁵R⁶, -COR⁵, and -CH₂(OR⁵);

R⁵ is selected from H, C₁-C₄ alkyl and PO₃H₂;

R⁶ is selected from H and C₁-C₄ alkyl; R⁷ is selected from -NR¹R² and -NO; and R¹⁰ is selected from H and -OR⁵;

such that the weight ratio of anti-inflammatory drug to purine derivative is from 10:1 to 1:4, said purine derivative being administered concurrently with the administration of said anti-inflammatory drug or no more than 30 minutes prior thereto.



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which under Rule 45 of the European Patent Convention
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0066918
Application number

EP 82 20 0618

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
XD	FR - M - 3894M (S.A. MAGSIFER) * Left-hand column, a) formule b)"propriétés pharmacologiques" --	1-9	A 61 K 31/62 31/70// (A 61 K 31/70 31/60)
X	UNLISTED DRUGS, vol. 19, no. 10, October 1967, Chatham, N.J. USA * Page 138e "Stornimed" *	1-9	
A	DE - A - 2 841 170 (PHARM. PRAPARATE APOTHEKER WALTER SCHOLZ) * Pages 1,2; claims 1,2,5 *	1-9	
AD	US - A - 3 089 869 (ROLAND YVES MAUVERNAY) -----	1-9	TECHNICAL FIELDS SEARCHED (Int. Cl. 3)
			A 61 K
INCOMPLETE SEARCH			
The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.			
Claims searched completely: 1-9			
Claims searched incompletely:			
Claims not searched: 10 Method for treatment of the			
Reason for the limitation of the search: human or animal body by			
surgery or therapy (see article 52 (4) of the			
European Patent Convention).			
Place of search	Date of completion of the search	Examiner	
The Hague	06-09-1982	BRINKMANN	
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X : particularly relevant if taken alone		T : theory or principle underlying the invention	
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